REMARKS/ARGUMENTS

I. Claim Status

Claim 15 has been amended to recite at least one complexing agent including sodium edetate. Claims 27, 38 and 51 have been amended to recite that the formulation also comprises at least one complexing agent. Support for these amendments is found on paragraph [0046] of the published application, namely U.S. Pub. No. 2004/0265238. The status of the claims are as follows:

Claims 3-4, 8-9, and 31 have been canceled.

Claims 6-7, 10-11, 17-20, 22-24, 33, 35-37 and 41-50 have been withdrawn.

Claims 1-2, 5, 12-16, 21, 25-30, 32, 38-40 and 51-69 are pending.

II. Rejections Under 35 USC §103(a)

To establish a prima facie case of obviousness the prior are references must teach or suggest each and every element claimed. The Office has not proven a *prima facie* case of obviousness because none of the references cited teach or suggest an inhalable formulation comprising the claimed concentration range of a hypertension reducing agent or a complexing agent, let alone the combination of the claimed concentration range and a complexing agent as recited in the currently amended claims.

Claims 1-2, 5, 12-16, 21, 25-30, 32, 34, 38-40 and 51-69 have been rejected under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent No. 5,554,610 to Williams et al. (hereinafter "Williams") in view of U.S. Publication No. 2006/0002992 to Schmehl et al. (hereinafter "Schmehl") or alternatively U.S. Patent No. 5,759,565 to Azaria et al. (hereinafter "Azaria") or alternatively in view of U.S. Publication No. 2001/0031738 to Schwarz (hereinafter "Schwarz").

A. The Cited References do not Teach or Suggest the Claimed Concentration Ranges

Williams is generally directed to methods of treating disorders associated with pulmonary hypertension by administering a given dose (mg) of a vasodilator either from one to four times per day. Specifically, Williams provides the following:

> [A] unit dose will normally contain 0.01 to 50 mg for example 0.01 to 10 mg, of the Compound, or a pharmaceutically acceptable salt thereof. Unit doses will normally be administered once or more than once a day, for example 2, 3, or 4 times a day, more

> usually 1 to 3 times a day such that the total daily dose is normally in the range of 0.0001 to 1 mg/kg...

See Williams at column 2, line 20 continuing through line 29. However, Williams does not explicitly teach or suggest a concentration range of 0.1 to 15 mg/ml as recited in Claims 1, 27, 38, and 51.

The Office acknowledges that "Williams does not explicitly disclose the concentration range in mg/ml," but contends that "it would have been obvious to one of ordinary skill in the art that the concentration of an active agent in a liquid base is disclosed in mg/ml." Therefore, the Office is asserting that Williams inherently teaches or suggests the currently claimed concentration ranges. Accordingly to MPEP 2112 (IV), the Office must provide the rationale or evidence to support a showing of inherency. Applicant respectfully submits that the Office has merely asserted the conclusory statement that since Williams teaches unit doses (mg) for inhalation, it would have been obvious to one of ordinary skill in the art that the concentration of an active agent in a liquid base is disclosed in mg/ml. Applicant submits that Williams does not inherently disclose the claimed concentrations.

"To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.' " *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999). "In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." *Ex parte Levy,* 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990). To the contrary, the Office has merely provided the statement that it would have been obvious to one of ordinary skill in the art that the concentration of an active agent in a liquid base is disclosed in mg/ml. The Office has not provided technical or factual basis to explain why the claimed concentration range is necessarily present in Williams as currently claimed. Applicant notes that Williams is silent regarding any suitable volumes for any corresponding dosage. As such the claimed

concentration range of a hypertension reducing agent is not necessarily present in Williams. Accordingly, Williams does not explicitly of inherently teach or suggest each an every element, namely the currently claimed concentration ranges, of independent claims 1, 27, 38 and 51.

In general, Schmehl is directed to liposomal formulations for pulmonary application, wherein the liposomes release encapsulated drug compounds in a controlled manner. Schmehl teaches that the frequency of administration of vasodilators for the treatment of pulmonary hypertension may be reduced by providing a sustained-release liposomal formulation. The liposome components, DPPC and cholesterol are present at a molar ratio of 7:3 and 7:4, respectively. Schmehl also provides the release kinetics from liposomes for carboxyfluorescein. However, Schmehl does not provide any discussion regarding concentration ranges of hypertension reducing agents, much less the claimed concentration range for a non-liposomal formulation. Accordingly, Schmehl does not teach of suggest the currently claimed concentration ranges recited or non-liposomal formulations as recited in independent claims 1, 27, 38 and 51.

Azaria is directed to galenic compositions for nasal administration including a calcitonin as the active agent. Calcitonins are long chain polypeptides used in the treatment of Paget's disease, hypercalcaemia and osteoporsis. The compositions described by Azaria are adapted for administration in the form of a nasal spray. However, Azaria is silent regarding hypertension reducing agents and concentration ranges of hypertension reducing agents for inhalable formulations. Accordingly, Azaria also does not teach or suggest the currently claimed concentration ranges.

Schwarz is directed to formulations for inhibiting endothelial-monocyte activating polypeptide II (EMAP II). More specifically, Schwarz is directed to a method of administering a formulation utilizing an active compound that "inhibits EMAP II activity, including compounds that specifically bind to EMAP II (e.g., an antibody), compounds that downregulate EMAP II expression (e.g., an antisense oligonucleotide), or EMAP II receptor antagonists." Schwarz generically discloses administering such an active compound either alone or in conjunction with another compound known to be useful in treating pulmonary hypertension such as a calcium-channel blocker, angiotensin-converting enzyme inhibitors, nitrous oxide, L-arginine, and

digoxin. Therefore, the formulations according to Schwarz must include a compound that inhibits EMAP II activity (e.g., an antibody, an antisense oligonucleotide, or a receptor antagonist). Schwarz provides some dosage teachings based on the active compound, wherein the active compound is one that inhibits EMAP II activity (e.g., an antibody, an antisense oligonucleotide, or a receptor antagonist). See page 3, paragraph 27. Therefore, Schwarz also fails to teach the concentration ranges for the hypertension reducing agents recited in independent claims 1, 27, 38 and 51.

Since the cited references all fail to teach or suggest the currently claimed concentration range of a hypertension reducing agent as recited in independent claims 1, 27, 38 and 51, any combination of Williams and Schmehl, Azaria or Schwarz also fails to teach or suggest the currently claimed range of a hypertension reducing agent. Applicant submits that the obviousness rejection has been overcome and requests withdrawal of this rejection.

B. The Cited References do not Teach or Suggest a Complexing Agent

Williams, Schmehl, Azaria and Schwarz are discussed in detail above. Not one of the cited references teaches or suggests a complexing agent, let alone the combination of the claimed concentration range and a complexing agent as recited in the currently amended claims. Furthermore, not one of the cited references teaches or suggests an inhalable formulation including any of the following complexing agents: sodium edetate (claim 15 and 51); ethylenediaminetertraacetic acid (claim 51), citric acid (claim 51) or nitrilotriacetic acid (claim 51).

All of the cited references simply do not teach or suggest an inhalable formulation including a complexing agent. Furthermore, not one of the references discusses the desirability of including a complexing agent in an inhalable formulation; much less the specific agents recited in claims 15 and 51. Accordingly, any combination of the cited references also fails to teach or suggest an inhalable formulation including a complexing agent. Therefore, Applicant submit that the obviousness rejection has been overcome and requests withdrawal of this rejection.

Since Williams, Schmehl, Azaria and Schwarz all fail to teach or suggest the following: (1) the currently claimed concentration range of a hypertension reducing agent; (2) an inhalable

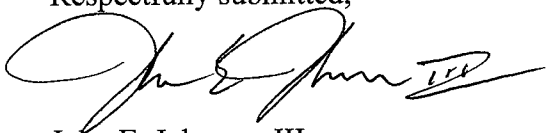
formulation including a complexing agent and (3) the combination of the claimed concentration range of a hypertension reducing agent and a complexing agent, any combination of Williams and Schmehl, Azaria or Schwarz also fails to teach or suggest these elements of the currently amended claims. Applicant submits that the obviousness rejection has been overcome and requests withdrawal of this rejection.

III. Conclusion

In view of the amendments and remarks made above, Applicant submits that the pending claims are now in condition for allowance. Applicant respectfully requests that the claims be allowed to issue. If the Examiner wishes to discuss the application or the comments herein, the Examiner is urged to contact the undersigned by telephone.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,



John E. Johnson, III
Registration No. 58,367

Customer No. 00826
ALSTON & BIRD LLP
Bank of America Plaza
101 South Tryon Street, Suite 4000
Charlotte, NC 28280-4000
Tel Charlotte Office (704) 444-1000
Fax Charlotte Office (704) 444-1111
LEGAL02/30318887v1

ELECTRONICALLY FILED USING THE EFS-WEB ELECTRONIC FILING SYSTEM OF THE UNITED STATES PATENT & TRADEMARK OFFICE ON APRIL 17, 2007.